Misfolded molecules gain prominence as culprits in aging

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Courtesy of the Salk Institute
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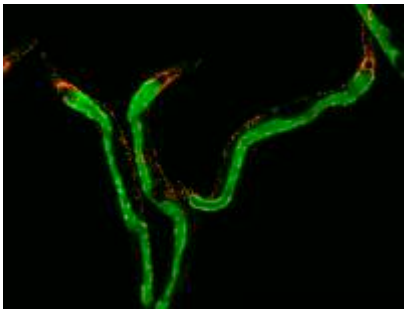
Misfolded biological molecules are under growing suspicion as major culprits in the aging process, according to scientists at the prestigious Salk Institute for Biological Studies in La Jolla, Calif.

This new thinking is emerging as an offshoot of a research approach that originally tended to see aging as a result of something akin to burning a candle at both ends. In this view, the chief problem was overactivity in cellular energy-generating compartments, called mitochondria.



Intestinal (green) and nerve (red) cells of the type studied in an analysis of mitochondrrial function and longevity at the Salk Institute. (Image courtesy K. Berendzen, Salk Institute for Biological Studies)

It turns out, though, that mitochondria are also involved in folding large molecules called proteins—which are ubiquitous throughout the body—into specific forms so that they can properly carry out their many functions.

Overactive mitochondria can lead to an increase in wrongly folded proteins, according to Andrew Dillin at the Salk Institute and colleagues, who report some of their latest research in the Jan. 7 issue of the journal *Cell*.

Using the roundworm *Caenorhabditis elegans* as a model organism, the group found that "perturbing" mitochondrial function in certain worm cells led to curious effects. The affected cells, Dillin explained, apparently sent a distress signal to other bodily tissues, which responded by launching a concerted campaign to fix misfolded proteins. This process seemed in turn to extend the worms' lifespan.

The "manipulation had to occur within a critical time window in a worm's lifespan to get the maximal effect," Dillin said, noting that effects were long-lasting. "It was like you could manipulate mitochondria in a 30-year-old human and get an extra 15 years, while in an 80-year-old, you might only gain two or three years."

The distress signals triggered a flurry of activity fixing misfolded proteins, known as the Unfolded Protein Response, Dillin explained. He describes it as a an emergency plan that cells launch when improperly folded proteins accumulate excessively, creating a toxic situation for cells. The Unfolded Protein Response mobilizes a team of "helper" molecular structures that, like sales clerks at a Gap sweater table, refold the errant proteins.

To bring about the distress signals in the first place, Dillin and colleagues experimentally inactivated a gene called cco-1 in worms. The gene is responsible for the production of a protein essential for chemical reactions collectively known as the Electron Transport Chain, which are required for mitochondria to generate energy—and thus, for cells to live.

The longevity effect worked for worms in which cco-1 inactivation affected cells in the intestine or nerve cells, the scientists found. And the effect vanished when the Unfolded Protein Response was

chemically blocked, they said, pointing to the crucial role of this response in the longevity effect.

The nature of the distress signal itself is unknown, Dillin said.

Before 2000, Dillin said, biology textbooks defined mitochondria solely in terms of energy production, “but we now recognize numerous other critical activities performed by mitochondria.” For longevity, “it all comes down to protein folding,” he added. “That’s become the unifying theme in my lab.”